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**Smek promotes corticogenesis through regulating Mbd3's stability and Mbd3/NuRD complex recruitment to genes associated with neurogenesis.**

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**Public Summary:**

The fate of neural progenitor cells (NPCs) during corticogenesis is determined by a complex interplay of genetic or epigenetic components, but the underlying mechanism is incompletely understood. Here, we demonstrate that Suppressor of Mek null (Smek) interact with methyl-CpG-binding domain 3 (Mbd3) and the complex plays a critical role in self-renewal and neuronal differentiation of NPCs. We found that Smek promotes Mbd3 polyubiquitylation and degradation, blocking recruitment of the repressive Mbd3/nucleosome remodeling and deacetylase (NuRD) complex at the neurogenesis-associated gene loci, and, as a consequence, increasing acetyl histone H3 activity and cortical neurogenesis. Furthermore, overexpression of Mbd3 significantly blocked neuronal differentiation of NPCs, and Mbd3 depletion rescued neurogenesis defects seen in Smek1/2 knockout mice. These results reveal a novel molecular mechanism underlying Smek/Mbd3/NuRD axis-mediated control of NPCs' self-renewal and neuronal differentiation during mammalian corticogenesis.

**Scientific Abstract:**

The fate of neural progenitor cells (NPCs) during corticogenesis is determined by a complex interplay of genetic or epigenetic components, but the underlying mechanism is incompletely understood. Here, we demonstrate that Suppressor of Mek null (Smek) interact with methyl-CpG-binding domain 3 (Mbd3) and the complex plays a critical role in self-renewal and neuronal differentiation of NPCs. We found that Smek promotes Mbd3 polyubiquitylation and degradation, blocking recruitment of the repressive Mbd3/nucleosome remodeling and deacetylase (NuRD) complex at the neurogenesis-associated gene loci, and, as a consequence, increasing acetyl histone H3 activity and cortical neurogenesis. Furthermore, overexpression of Mbd3 significantly blocked neuronal differentiation of NPCs, and Mbd3 depletion rescued neurogenesis defects seen in Smek1/2 knockout mice. These results reveal a novel molecular mechanism underlying Smek/Mbd3/NuRD axis-mediated control of NPCs' self-renewal and neuronal differentiation during mammalian corticogenesis.

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